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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/447,218	11/23/1999	A.K. GUNNAR ABERG	4821-362	3537

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EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/447,218	ABERG ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 20, 2004 (Response)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-40,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-40,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: ~~See Continuation Sheet~~.

No claims have been cancelled, no claims have been amended, the disclosure has not been amended, and no new claims have been added as per the response filed August 20, 2004. No additional Information Disclosure Statements (IDSs) have been received. Newly submitted references/exhibits have been made of record on the attached PTO-892. Applicant's submission of new references is noted. Each new reference has been cited on the PTO-892. However, in order to insure that examiner has the benefit of a complete and unambiguous reading of the **Brandes et al.** reference, examiner respectfully requests a new copy be provided with the next response because the present copy kindly FAXed to examiner by applicant does not include all of the text at the right margin throughout the reference.

Note to applicant: A new type of PTO-892 has been introduced by the PTO which does not yet permit complete disclosure of lengthy non-patent literature citations at present. Therefore, in order to facilitate applicant's reading and understanding of the instant Office action, a copy of the original and complete PTO-892 as presently updated has been attached to the paper copy of the new form and includes all of the identifying designations (**R**, **S**, **T**, etc.) of the references already of record and those newly provided as referred to in the present Office action.

Claims **34-40 and 48-49** remain in the case.

Claims **35, 37, 48 and 49** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims **35, 37 and 48** fail to further limit independent claim **34** because the stated limitations in each claim are not accompanied in either claim by a further procedural step or steps. And additionally claim **36** is indefinite for failure to define which particular "cancer/cancers" is/are to be avoided, an important question in light of the wide variation in the severity and etiology of neoplastic disease conditions. Also claim **49** is incomplete for failure to specify the step or steps to be taken to determine the particular hosts who should avoid the instant method of treatment.

Applicant's arguments filed August 20, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant argues that it is unnecessary to name particular drugs to be avoided. However, claim **37** does not clearly indicate that "avoiding" means the -- avoidance of administering the claimed active ingredient together with -- the specified class of active ingredient is the intended additional "step." Appropriate amendment to make the intended meaning clear is respectfully requested.

Claims **35, 48 and 49** fail to further limit the subject matter of independent claim **34** because the noted dependent claims make reference to side effects that are inherently avoided when the active ingredient DCL is administered and are therefore already part of the independent claim. For this reason cancellation of the noted claims is respectfully requested.

Claim **37** is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims extends in the noted claim to the alleged necessity to avoid administration of DCL along with another active ingredient which "inhibits cytochrome P450."

B. The nature of the invention is directed to the administration of DCL to treat urticaria (hives) in a human host in need thereof including the negative limitation provided in claim **37** and summarized in the previous paragraph.

C. The state of the prior art does not include any data in support of the alleged need to avoid administration of DCL with other active ingredients known to cause inhibition of cytochrome P-450.

D. The level of one of ordinary skill is low because there is no known disclosed basis for determining which active ingredients which inhibit cytochrome P450 must be avoided when administering DCL to treat urticaria.

E. The level of predictability in the art is low because of the lack of data in re DCL and the effect of coadministration of other active ingredients of the kind specified. The necessary data is neither disclosed in the prior art nor disclosed herein.

F. The amount of direction provided by the inventor is limited to a prospective disclosure of test data but no actual data has been provided.

G. The existence of working examples is limited to a prospective disclosure; i.e. there are no working examples to provide a factual basis for the limitation of claim **37**.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive because of the lack of adequate guidance concerning the need to avoid administration of any other active ingredients including those generically specified by claim **37**. In particular the instant disclosure does not disclose non-prospective examples of "other" active ingredients known to inhibit cytochrome P450 and the actual practice of the claimed invention including data showing the effects of the presence, and the absence, of any specific "other" active ingredient on cells in culture or other living hosts being treated for urticaria.

Applicant's arguments with respect to claim **34-40 and 48-49** have been considered but are deemed to be moot in view of the new grounds of rejection.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **34-40, 48 and 49** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Berkow et al.** (PTO-892 ref. **R**) in view of **Villani et al. '716** (PTO-1449 ref. **AE**).

The instant claims are directed to the treatment of urticaria (aka hives) by the administration of an effective dosage of descarboethoxyloratadine (DCL) to a patient in need

thereof. The dosage is further defined as 0.1 mg to less than about 10 mg per day or less than about 5 mg per day.

Berkow et al. discloses at p. 333, beginning in the third line under "**Treatment**," that " [s]ymptoms [of urticaria] usually can be relieved with an oral [dose of an] antihistamine ... ."

Villani et al. '716 discloses at column 1, lines 39-46 that descarboethoxyloratadine (DCL) and closely related compounds are effective antihistamines with the advantage of low CNS-related side effects, i.e. that DCL and relatives are non-sedative. Villani also discloses at column 8, lines 11-46 that the dosage range is about 1 mg to 40 mg for a 24 hour period and preferably from about 5 to about 10 mg over this time period (column 8, line 19) More generally the unit dosage is defined as "from 1 mg to 1000 mg according to the particular application" (column 8, lines 43-44).

The findings that
i) Villani et al.'s teaching that DCL and related compounds are known to be effective antihistamines,
ii) the teaching by applicant that DCL has the expected effect in the treatment of urticaria (hives) as predicted by Berkow et al.,
iii) the teaching of dosages ranges which overlap with the claimed dosage ranges, and
iv) the failure of applicant to establish statistically significant unexpected results (no error analysis of the data provided),
when taken together with the disclosure of Berkow et al. are deemed to establish that combination of the instant combination of references is properly motivated. These particular disclosures are also deemed to render the instant claimed subject matter lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claims directed to treatment of urticaria by the administration of the antihistamine DCL, including within the dosage ranges of the instant dependent claims, would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed August 20, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant argues that the Berkow reference specifies that urticaria *must be treated with* one of the three antihistamines listed on page 333. Examiner respectfully disagrees. Applicant's attention is drawn to the term "eg" which precedes the listing, a term which the dictionary defines as meaning-- for example --. Applicant is also respectfully requested to note that the Berkow disclosure is not limited to three active ingredients, but lists a total of 5 different compounds, including one which is a single member of the generic class "glucocorticoid," which are known in the art to be effective in the treatment of urticaria in its various forms and manifestations. Therefore, based on a careful reading of Berkow, applicant's assertion that Berkow strictly limits its guidance to the three listed antihistamines is deemed to be incorrect. Applicant notes additional references submitted with a previous communication and argues that each destroys the credibility of the Berkow et al teaching. Berkow's disclosure is much longer and more nuanced that applicant's argument suggests; e.g comments at the tp of page 334 make it clear that the treatment of urticaria is a complicated subject, that the listed agents useful for treatment do not always work in every patient, and that there are various types of urticaria including "chronic urticaria" and urticaria in children which respond differently to different active ingredients. The view that a complete knowledge of how to treat each and every case of urticaria was not known by Berkow et al. is confirmed by the references kindly supplied by applicant. For example, examiner notes that the **Simons et al.** reference (PTO-1449 ref. **CM**) also lists at p. 1666 in Table 2 both first and second generation anti-histamines and the recommended dosages for various classes of patients, but does not assert on the noted page or on any other page that there is only one best treatment for any one patient or class of patients suffering from urticaria. For these reasons applicant's arguments have not been found convincing and the above grounds of rejection has therefore been maintained.

Claims **34-40, 48 and 49** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Swinyard (II)** (PTO-892 ref. **TA**) and **Swinyard (I)** (PTO-892 ref. **SA**) in view of **Villani et al. '716** (PTO-1449 ref. **AE**) and further in view of **Brandes et al.** (PTO-892 ref. **RA**).

The instant claims are directed to the treatment of urticaria (aka hives) by the administration of an effective dosage of descarboethoxyloratadine (DCL) to a patient in need thereof and avoidance of the side effects thereof. The dosage is further defined as 0.1 mg to less than about 10 mg per day or less than about 5 mg per day.

Swinyard (II) discloses the utility of H_1-antihistamines in the treatment of urticaria at page 1124, column 1, line 4 of the third paragraph following the heading "Antihistamines." And at page 1130, column 2, this reference discloses the antihistamine azatadine maleate which is a very close structural relative of both loratadine and descarbethoxyloratadine (DCL), sharing with both the identical four ring molecular skeleton and similar antihistamine activity.

Swinyard (II) discloses at pages 778-782 (see page 779, paragraph beginning at column 1) that only certain H_2-antihistamines cause problems with liver P450 enzyme metabolism, but that selection of an alternative H_2-antihistamine is an effective way to avoid this difficulty.

Villani et al. '716 discloses at column 1, lines 39-46 that descarboethoxyloratadine (DCL) and closely related compounds are effective antihistamines with the advantage of low CNS-related side effects, i.e. that DCL and relatives are non-sedative. Villani also discloses at column 8, lines 11-46 that the dosage range is about 1 mg to 40 mg for a 24 hour period and preferably from about 5 to about 10 mg over this time period (column 8, line 19) More generally the unit dosage is defined as "from 1 mg to 1000 mg according to the particular application" (column 8, lines 43-44).

Brandes et al. discloses in the last sentence prior to the "CONCLUSION" that loratadine promotes the growth of two well known neoplasms. This issue is addressed by the instant disclosure at page 24, lines 20-25, with data which is at best incomplete because only one comparison is made and because there is no statistical error analysis permitting determination of whether the difference suggested by the data is statistically significant.

The motivation to combine the above references is that each is directed to positive and/or negative effects observed following the administration of antihistamines. The primary reference, Swinyard (II) clearly is well motivated in combinations with the remaining references, because this reference discloses all of the side effects commonly associated with H_1-antihistamine administration, and how these may be avoided by substitution of alternative antihistamines, including an antihistamine which is a close structural relative of both loratadine and DCL.

The substitution of DCL for loratadine or its analogue azatadine is deemed to have been an obvious substitution of the ordinary practitioner seeking to optimize the treatment of urticaria as reported in Swinyard (II) in view of the disclosure of Villani et al. that DCL is, like

loratadine, also an antihistamine. The additional guidance provided by the Swinyard (I) and Brandes references merely adds to the already extensive discussion in Swinyard (II) of the side effects observed following administration of medicinally appropriate dosages of numerous antihistamines, and therefore would have afforded the ordinary practitioner more than sufficient guidance to make an appropriate determination of whether or not to use DCL to treat urticaria in a given human host in need thereof. These particular disclosures are also deemed to render the instant claimed subject matter lacking in any patentable distinction in view of the noted combination of prior art.

Therefore, the instant claims directed to treatment of urticaria by the administration of the antihistamine DCL when appropriate lin light of possible side effects, including within the dosage ranges of the instant dependent claims, would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments with respect to claims **34-40 and 48-49** have been considered but are deemed to be moot in view of the new grounds of rejection.

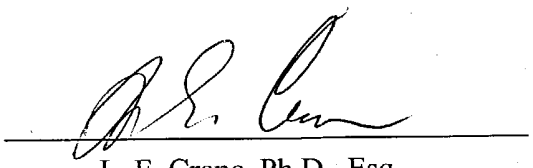
Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
11/15/2004



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